DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Concordia Pharmaceuticals Inc.
Attn: Sheila Ehrenberg
Associate Director, U.S. Regulatory Affairs
OptumInsight Life Sciences Inc. [U.S. Agent for Concordia Pharmaceuticals Inc.]
131 Morristown Road
Basking Ridge, NJ 07920

RE: NDA 022331
KAPVAY™ (clonidine hydrochloride) extended-release tablets
MA #133

Dear Ms. Ehrenberg:

This letter notifies Concordia Pharmaceuticals Inc. (Concordia), that the Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed a professional telephone script (V4_06_20_2013) (script) for KAPVAY™ (clonidine hydrochloride) extended-release tablets (Kapvay) submitted by Concordia under cover of Form FDA 2253. The script is false or misleading because it omits important risk information associated with the use of Kapvay and omits material facts. Thus the script misbrands Kapvay within the meaning of the Federal Food, Drug and Cosmetic Act (FD&C Act), and makes its distribution violative. 21 U.S.C. 352(n); 321(n); 331(a); 21 CFR 202.1(e)(5)(i), (iii). Concordia also did not comply with 21 CFR 202.1(b)(1).

Background

Below are the indication and summary of the most serious and most common risks associated with the use of Kapvay.[1]

According to its FDA-approved product labeling (PI), Kapvay is indicated for the treatment of attention deficit hyperactivity disorder (ADHD) as monotherapy and as adjunctive therapy to stimulant medications. The INDICATIONS AND USAGE section of the PI also includes information regarding long term use, special diagnostic considerations and the need for comprehensive treatment.

Kapvay is associated with a number of serious risks. Kapvay is contraindicated in patients with known hypersensitivity to clonidine. The PI also contains Warnings and Precautions regarding the risks of hypotension/bradycardia, sedation and somnolence, abrupt discontinuation, allergic reactions, cardiac conduction abnormalities, and concomitant administration with other clonidine containing products.

[1] This information is for background purposes only and does not necessarily represent the risk information that should be included in the promotional piece cited in this letter.

In addition, the most common adverse reactions reported with the use of Kapvay include somnolence, fatigue, upper respiratory tract infection, irritability, throat pain, insomnia, nightmares, emotional disorder, constipation, nasal congestion, increased body temperature, dry mouth, and ear pain.

Omission of Risk Information

Promotional materials are misleading if they fail to reveal facts that are material in light of representations made or with respect to consequences that may result from the use of the drug as recommended or suggested by the materials. The script is misleading because it includes efficacy claims for Kapvay, but fails to include important risk information associated with the drug. Specifically, the script completely omits the contraindication, all of the warnings and precautions, and common adverse reactions associated with the use of Kapvay (see background section above). We note that the script includes a general statement about adverse events in the Add-On trial and the statement, "I can email the full prescribing information for *Kapvay* or you can also access it at the *Kapvay* website www.kapvay.com. Which do you prefer?" However, this does not mitigate the omission of the important risk information.

By omitting important risk information associated with Kapvay, the script misleadingly suggests that Kapvay is safer than has been demonstrated.

Omission of Material Facts

The script includes the claims, "*KAPVAY,* a treatment for ADHD," and "*KAPVAY*, a medication used to treat ADHD," but it is misleading because it fails to communicate material information regarding Kapvay's FDA-approved indication. Specifically, it omits the following material information from the INDICATIONS AND USAGE section of the PI (in pertinent part):

> Need for Comprehensive Treatment program
> KAPVAY is indicated as an integral part of a total treatment program for ADHD that may include other measures (psychological, educational, and social) for patients with this syndrome. . . .

In addition, the script includes the claim, "Doses should be taken twice a day, with either an equal or higher split dosage being given at bedtime" to describe the dosing and administration of this product. However, within the context of this script directed to healthcare professionals, this claim is misleading because it omits important material information necessary for the initial use of this product. Specifically, the DOSAGE AND ADMINISTRATION section of the PI states, "Dosing should be initiated with one 0.1 mg tablet at bedtime, and the daily dosage should be adjusted in increments of 0.1 mg/day at weekly intervals until the desired response is achieved."

Inadequate Presentation of Established Name

The script fails to disclose the established name (clonidine hydrochloride) in direct conjunction with the proprietary name (KAPVAY), as required by 21 CFR 202.1(b)(1).

Conclusion and Requested Action

For the reasons discussed above, the script misbrands Kapvay within the meaning of the FD&C Act, and makes its distributive violative. 21 U.S.C. 352(n); 321(n); 331(a); 21 CFR 202.1(e)(5)(i), (iii). Furthermore, Concordia did not comply with 21 CFR 202.1(b)(1).

OPDP requests that Concordia immediately cease violating the FD&C Act, as discussed above. Please submit a written response to this letter on or before July 21, 2014, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Kapvay that contain presentations such as those described above, and explaining your plan for discontinuing use of such materials.

Please direct your response to the undersigned at the **Food and Drug Administration, Center for Drug Evaluation and Research, Office of Prescription Drug Promotion, 5901-B Ammendale Road, Beltsville, Maryland 20705-1266** or by facsimile at (301) 847-8444. To ensure timely delivery of your submissions, please use the full address above and include a prominent directional notation (e.g. a sticker) to indicate that the submission is intended for OPDP. Please refer to MA #133 in addition to the NDA number in all future correspondence relating to this particular matter. All correspondence should include a subject line that clearly identifies the submission as a Response to an Untitled Letter. OPDP reminds you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your distribution of Kapvay complies with each applicable requirement of the FD&C Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Nazia Fatima, Pharm.D, MBA
Regulatory Review Officer
Office of Prescription Drug Promotion

{See appended electronic signature page}

Mathilda Fienkeng, Pharm.D
Team Leader
Office of Prescription Drug Promotion

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NAZIA FATIMA
07/07/2014

MATHILDA K FIENKENG
07/07/2014